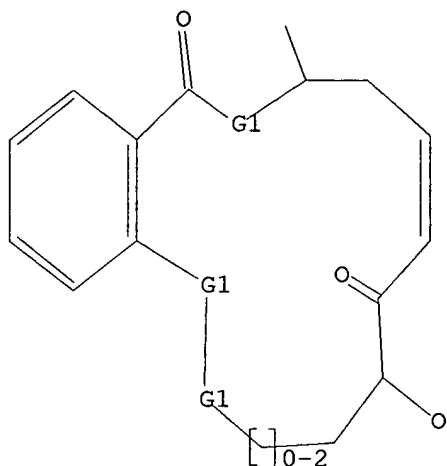


STR

1/23/2005



G1 C,O,N,S

Structure attributes must be viewed using STN Express query preparation.

=> s l1 sss full

FULL SEARCH INITIATED 17:47:57 FILE 'REGISTRY'

FULL SCREEN SEARCH COMPLETED - 477577 TO ITERATE

83.8% PROCESSED 400000 ITERATIONS

19 ANSWERS

INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)

SEARCH TIME: 00.00.06

FULL FILE PROJECTIONS: ONLINE **INCOMPLETE**
BATCH **COMPLETE**

PROJECTED ITERATIONS: 477577 TO 477577

PROJECTED ANSWERS: 19 TO 36

L2 19 SEA SSS FUL L1

=> file caplus

COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
161.33	161.54

FULL ESTIMATED COST

FILE 'CAPLUS' ENTERED AT 17:48:11 ON 23 JAN 2005

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

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FILE COVERS 1907 - 23 Jan 2005 VOL 142 ISS 5

FILE LAST UPDATED: 21 Jan 2005 (20050121/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s 12

L3 19 L2

=> d l3 1-19 ibib abs hitstr

L3 ANSWER 1 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:1038674 CAPLUS

DOCUMENT NUMBER: 142:11671

TITLE: Methods and compositions comprising an ubiquitin activator for inhibiting narrowing in mammalian vascular pathways

INVENTOR(S): Tremble, Patrice

PATENT ASSIGNEE(S): Medtronic Vascular, Inc., USA

SOURCE: U.S. Pat. Appl. Publ., 16 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004243224	A1	20041202	US 2004-818786	20040405
PRIORITY APPLN. INFO.:			US 2003-460366P	P 20030403

AB Methods and related compns. for treating vascular occlusions and preventing vascular narrowing are disclosed. In one embodiment an implantable medical device is provided with a coating comprising at least one cell growth inhibiting ubiquitin activator. In another embodiment a micro syringe is provided that injects the cell growth inhibiting ubiquitin activator directly into the adventitia. One specific embodiment includes a vascular stent having a cell growth inhibiting ubiquitin activator, specifically, hypothemycin. For example, to a solution of 250 µg of cell growth inhibiting ubiquitin activator in 27.56 mL of THF (THF), 251.6 mg of polycaprolactone was added forming a coating solution. The cleaned, dried stainless steel stents were coated by either spraying or by dipping into the cell growth inhibiting ubiquitin activator/polymer medicament solution to achieve a final coating weight of approx. 10 µg to 1 mg.

IT 76958-67-3, Hypothemycin

RL: DEV (Device component use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

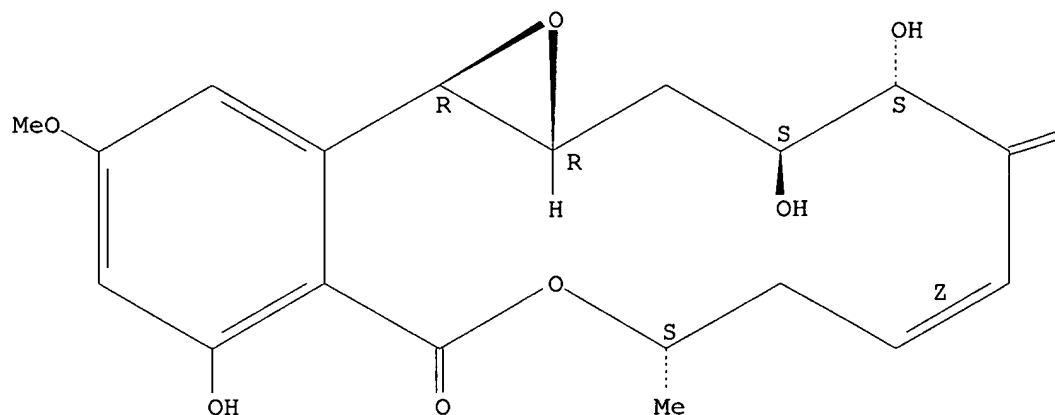
(compns. and devices comprising antiproliferative ubiquitin activator for treatment of vascular occlusions)

RN 76958-67-3 CAPLUS

CN 3H-Oxireno[k][2]benzoxacyclotetradecin-5,11(2H,4H)-dione, 1a,8,9,15b-tetrahydro-3,4,12-trihydroxy-14-methoxy-9-methyl-, (1aR,3S,4S,6Z,9S,15bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

Double bond geometry as shown.



=O

L3 ANSWER 2 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:964817 CAPLUS

DOCUMENT NUMBER: 141:410756

TITLE: Preparation of macrocyclic compounds for the treatment of inflammation and autoimmune disorders

INVENTOR(S): Chiba, Kenichi; Du, Hong; Eguchi, Yoshihito; Fujita, Masanori; Goto, Masaki; Gusovsky, Fabian; Harmange, Jean-Christophe; Inoue, Atsushi; Kawada, Megumi; Kawai, Takatoshi; Kawakami, Yoshiyuki; Kimura, Akifumi; Kotake, Makoto; Kuboi, Yoshikazu; Matsushima, Tomohiro; Mizui, Yoshiharu; Muramoto, Kenzo; Sakurai, Hideki; Shen, Yong-chun; Shirota, Hiroshi; Spyvee, Mark; Tanaka, Isao; Wang, John; Wood, Ray; Yamamoto, Satoshi; Yoneda, Naoki

PATENT ASSIGNEE(S): Japan

SOURCE: U.S. Pat. Appl. Publ., 299 pp., Cont.-in-part of Appl. No. PCT/US03/07377.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004224936	A1	20041111	US 2003-657910	20030909
WO 2003076424	A1	20030918	WO 2003-US7377	20030307

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

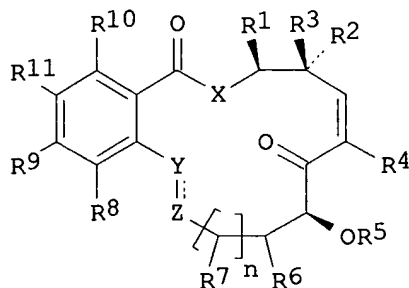
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,

KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
 FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

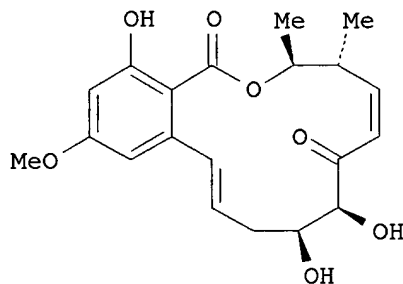
PRIORITY APPLN. INFO.:

US 2002-362883P P 20020308
 US 2002-380711P P 20020514
 WO 2003-US7377 A2 20030307

GI



I



II

AB Macrocyclic compds. of formula I [R1 = H, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, etc.; R2, R3 = H, halo, (substituted) OH, alkyl, aryl, etc.; R1R2, R1R3 = alkylene; R4 = H, halo; R5 = H, protecting group, prodrug; R6, R7, R11 = H, (substituted) OH; R8, R9 = H, halo, (substituted) OH, alkoxy, etc.; R10 = H, (substituted) OH, (substituted) NH2; n = 0-2; X = absent, O, NH, N-alkyl, CH2, S; Y, Z = CH, O, CO, NH, etc.] are prepared for the treatment of various disorders including inflammatory or autoimmune disorders, and disorders involving malignancy or increased angiogenesis. In certain embodiments, methods for the treatment of various disorders including inflammatory or autoimmune disorders comprise systemically (e.g., orally) administering to a subject in need thereof a therapeutically effective amount of a compound of formula I. Thus, II was prepared in several steps. Some of the compds. inhibited NF-κB with IC50 values < 10μM.

IT 603045-43-8P 791101-06-9P 791101-07-0P
 791101-08-1P 791101-09-2P 791101-10-5P
 791807-02-8P

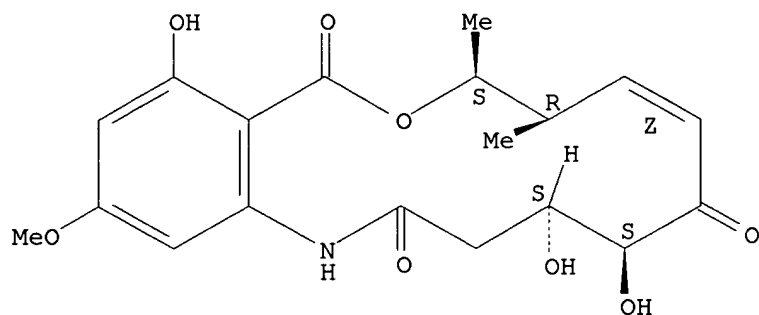
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of macrocyclic compds. for the treatment of inflammatory or autoimmune disorders)

RN 603045-43-8 CAPLUS

CN 2H-11,1-Benzoxaazacyclotetradecine-2,6,12(1H,3H)-trione,
 4,5,9,10-tetrahydro-4,5,13-trihydroxy-15-methoxy-9,10-dimethyl-,
 (4S,5S,7Z,9R,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.



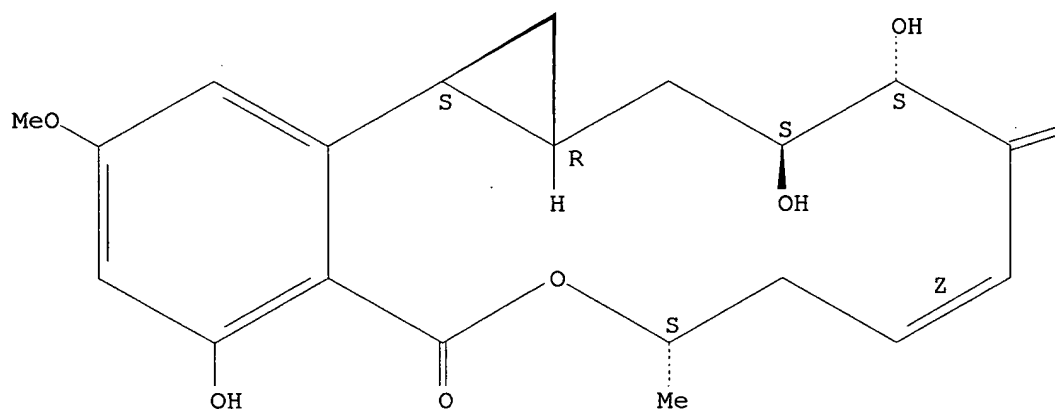
RN 791101-06-9 CAPLUS

CN Benzo[c]cycloprop[e]oxacyclotetradecin-5,11-dione, 7,8,12,13,14,14a,15,15a-octahydro-4,12,13-trihydroxy-2-methoxy-7-methyl-, (7S,9Z,12S,13S,14aR,15aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

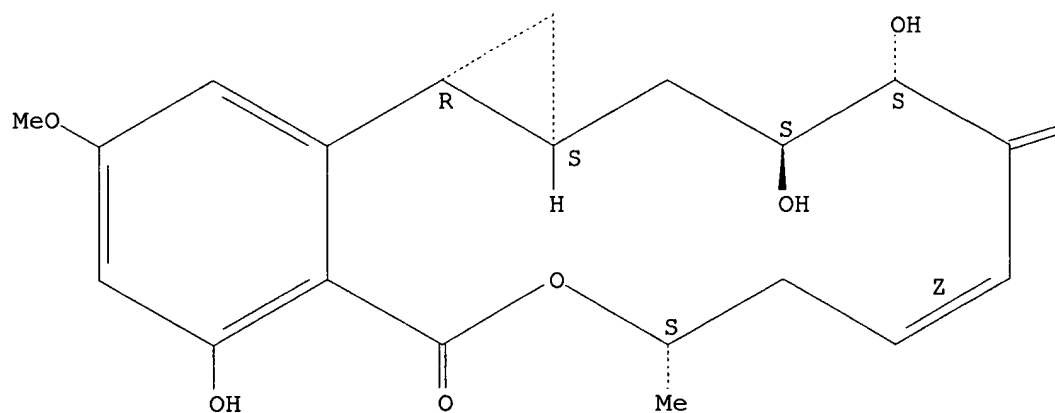
=O

RN 791101-07-0 CAPLUS

CN Benzo[c]cycloprop[e]oxacyclotetradecin-5,11-dione, 7,8,12,13,14,14a,15,15a-octahydro-4,12,13-trihydroxy-2-methoxy-7-methyl-, (7S,9Z,12S,13S,14aS,15aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

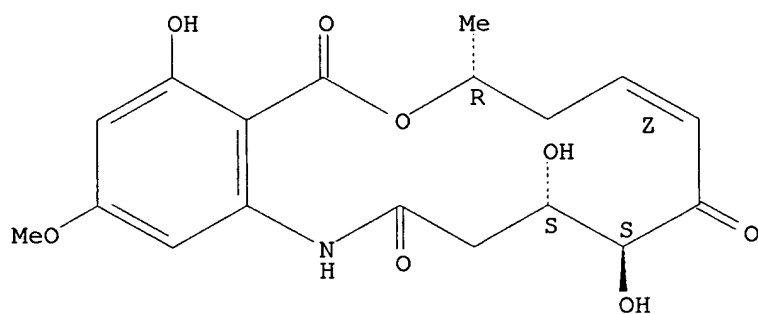
Double bond geometry as shown.



$\equiv O$

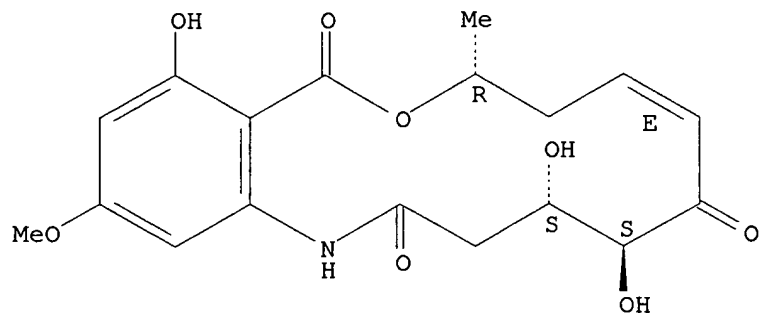
RN 791101-08-1 CAPLUS
 CN 2H-11,1-Benzoxaazacyclotetradecine-2,6,12(1H,3H)-trione,
 4,5,9,10-tetrahydro-4,5,13-trihydroxy-15-methoxy-10-methyl-,
 (4S,5S,7Z,10R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.



RN 791101-09-2 CAPLUS
 CN 2H-11,1-Benzoxaazacyclotetradecine-2,6,12(1H,3H)-trione,
 4,5,9,10-tetrahydro-4,5,13-trihydroxy-15-methoxy-10-methyl-,
 (4S,5S,7E,10R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as described by E or Z.

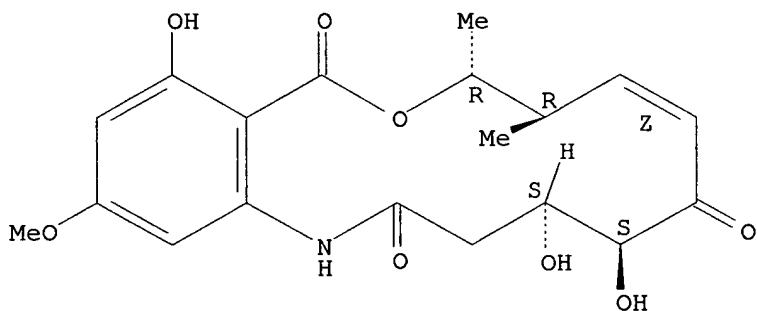


RN 791101-10-5 CAPLUS

CN 2H-11,1-Benzoxaazacyclotetradecine-2,6,12(1H,3H)-trione,
4,5,9,10-tetrahydro-4,5,13-trihydroxy-15-methoxy-9,10-dimethyl-,
(4S,5S,7Z,9R,10R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry as shown.

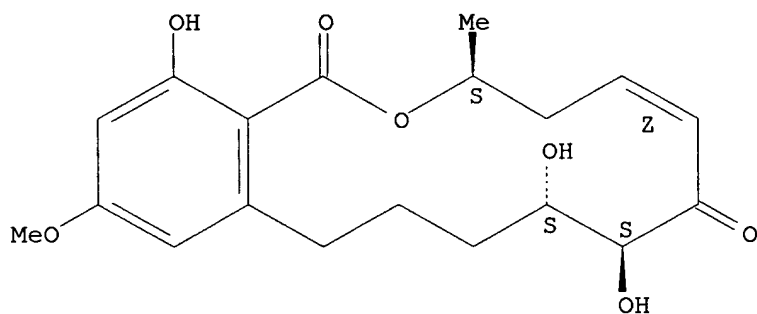


RN 791807-02-8 CAPLUS

CN 1H-2-Benzoxacyclotetradecin-1,7(8H)-dione, 3,4,9,10,11,12-hexahydro-8,9,16-
trihydroxy-14-methoxy-3-methyl-, (3S,5Z,8S,9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry as shown.



L3 ANSWER 3 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN

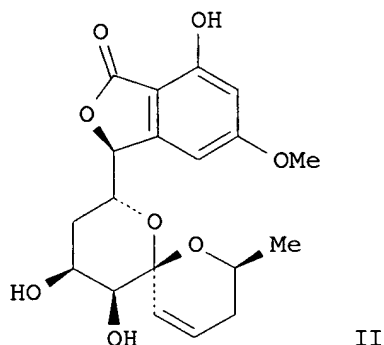
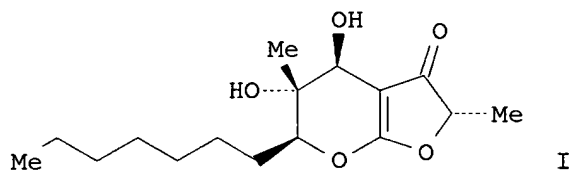
ACCESSION NUMBER: 2004:42365 CAPLUS

DOCUMENT NUMBER: 140:213678

TITLE: Ketene acetal and spiroacetal constituents of the
marine fungus *Aigialus parvus* BCC 5311

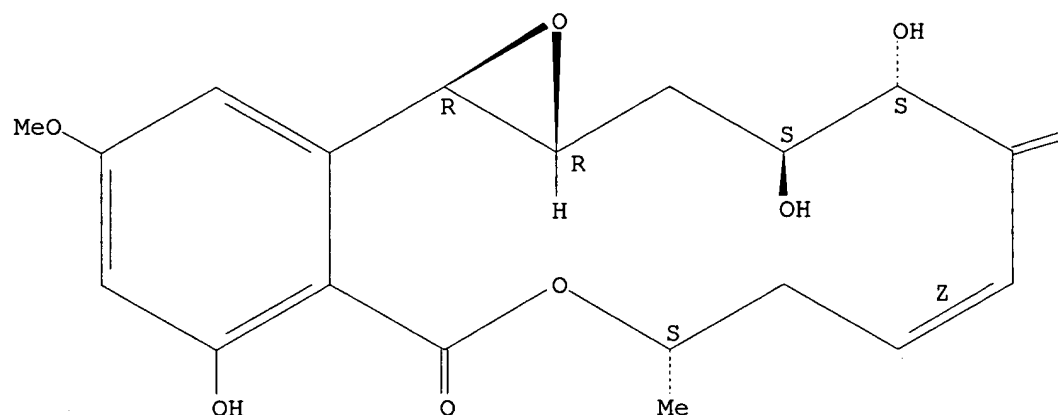
AUTHOR(S): Vongvilai, Pornrapee; Isaka, Masahiko; Kittakoop,
Prasat; Srikitikulchai, Prasert; Kongsaree,

CORPORATE SOURCE: Palangpon; Thebtaranonth, Yodhathai
 Department of Chemistry, Faculty of Science, Mahidol
 University, Bangkok, 10400, Thailand
 SOURCE: Journal of Natural Products (2004), 67(3), 457-460
 CODEN: JNPRDF; ISSN: 0163-3864
 PUBLISHER: American Chemical Society
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 GI



- AB Aigialone (I) and aigialospirol (II), two structurally unique compds., were isolated from the mangrove fungus *Aigialus parvus* BCC 5311. The structure of I was elucidated by spectral anal., and its relative stereochem. was determined by X-ray crystallog. The stereochem. of II, elucidated by NMR spectral anal., suggested that this compound is possibly derived from hypothemycin, a metabolite previously isolated from this same fungus.
- IT **76958-67-3**, Hypothemycin
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (constituents of the marine fungus *Aigialus parvus* BCC 5311)
- RN 76958-67-3 CAPLUS
- CN 3H-Oxireno[k][2]benzoxacyclotetradecin-5,11(2H,4H)-dione,
 1a,8,9,15b-tetrahydro-3,4,12-trihydroxy-14-methoxy-9-methyl-,
 (1aR,3S,4S,6Z,9S,15bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
 Double bond geometry as shown.



=O

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2004:41213 CAPLUS
 DOCUMENT NUMBER: 140:105249
 TITLE: Combination of mTOR inhibitor and a tyrosine kinase inhibitor for the treatment of neoplasms
 INVENTOR(S): Neel, Benjamin G.; Mohi, Golam
 PATENT ASSIGNEE(S): Beth Israel Deaconess Medical Center, USA
 SOURCE: PCT Int. Appl., 63 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004004644	A2	20040115	WO 2003-US20972	20030703
WO 2004004644	A3	20040506		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-394029P P 20020705
 US 2002-412402P P 20020920

AB The invention features methods and compns. including an mTOR inhibitor and a tyrosine kinase inhibitor for reducing the proliferation of and

enhancing the apoptosis of neoplastic cells. The addition of an MEK inhibitor to this combination further enhances the effectiveness of this therapeutic method.

IT 219917-92-7, L 783277

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(L 783277; combination of mTOR inhibitor and tyrosine kinase inhibitor for cancer therapy)

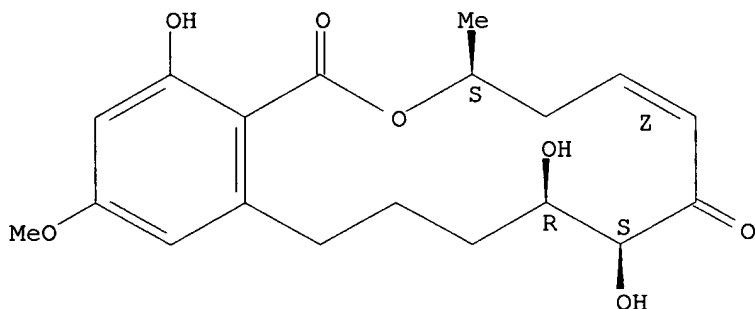
RN 219917-92-7 CAPLUS

CN 1H-2-Benzoxacyclotetradecin-1,7(8H)-dione, 3,4,9,10,11,12-hexahydro-8,9,16-trihydroxy-14-methoxy-3-methyl-, (3R,5Z,8R,9S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

Double bond geometry as shown.

Currently available stereo shown.



L3 ANSWER 5 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:737744 CAPLUS

DOCUMENT NUMBER: 139:261090

TITLE: Preparation of macrocyclic compounds for use in pharmaceutical and cosmetic compositions which regulate various genes involved in immune and inflammatory responses

INVENTOR(S): Boivin, Roch; Chiba, Kenichi; Davis, Heather A.; Diepitro, Lucian; Du, Hong; Eguchi, Yoshihito; Fujita, Masanori; Gilbert, Sandra; Goto, Masaki; Harmange, Jean Christophe; Inoue, Atsushi; Jiang, Yimin; Kawada, Megumi; Kawai, Takatoshi; Kawakami, Yoshiyuki; Kimura, Akifumi; Kotake, Makoto; Kuboi, Yoshikazu; Lemelin, Charles; Li, Xiang-yi; Matsushima, Tomohiro; Mizui, Yoshiharu; Sakurai, Hideki; Schiller, Shawn; Shen, Yongchun; Spyvee, Mark; Tanaka, Isao; Wang, Yuan; Yamamoto, Satoshi; Yoneda, Naoki; Kobayashi, Seiichi

PATENT ASSIGNEE(S): Eisai Co. Ltd., Japan; et al.

SOURCE: PCT Int. Appl., 438 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

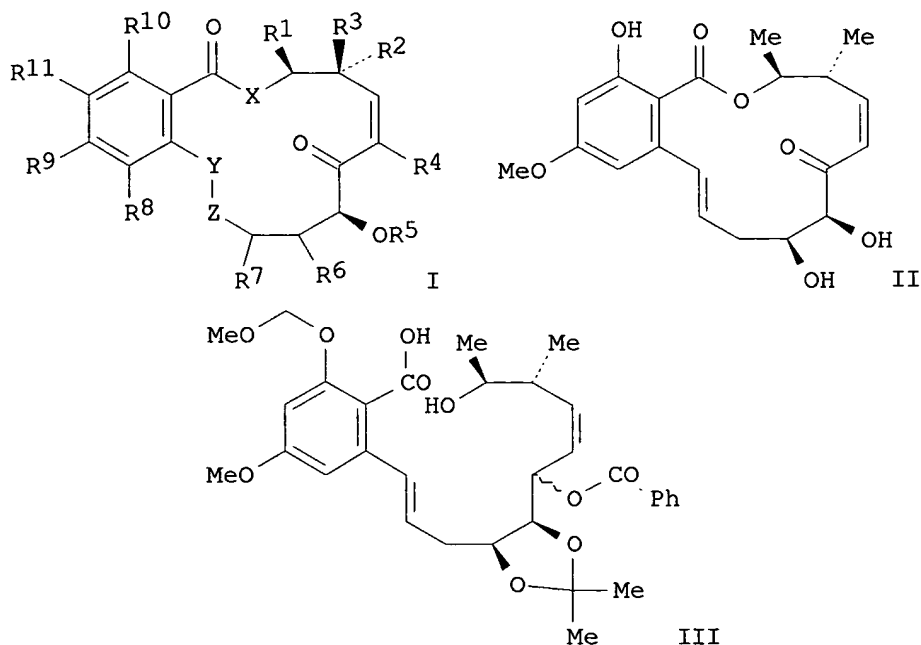
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003076424	A1	20030918	WO 2003-US7377	20030307
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,				

PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,
 UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
 KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
 FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004224936 A1 20041111 US 2003-657910 20030909
 PRIORITY APPLN. INFO.: US 2002-362883P P 20020308
 US 2002-380711P P 20020514
 WO 2003-US7377 A2 20030307

OTHER SOURCE(S): MARPAT 139:261090
 GI



AB Macrocyclic lactones and lactams, such as I [R1 = H, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl; R2, R3 = H, OH, halogen, protected hydroxyl, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl; R1R2 or R1R3 = 3-8 membered alicyclic ring; R4 = H, halogen; R5 = H, hydroxyl protecting group, linked prodrug; R6, R7 = H, OH, protected hydroxyl; R8, R9, R10, R11 = H, OH, NH2, alkoxy, alkylamino, etc.; X = O, NH, S, CH2, etc.; R8R9 = fused ring, such as furan or imidazole; Y-Z = CH:CH, NHCO, etc.], were prepared for a variety of therapeutic and cosmetic uses, such as antitumor and anti-inflammatory agents and treatment of skin photodamage. These macrocycles are claimed for use as NF- κ B, AP-1, protein kinase, cancer cell proliferation and solid tumor angiogenesis inhibitors and for use in the treatment of inflammation, cancer, psoriasis, skin photodamage, restenosis as stent coatings, rheumatoid arthritis, asthma, sepsis, inflammatory bowel disease, atopic dermatitis, Crohn's disease, autoimmune disorders and for treatment of gastrointestinal, esophageal, tracheal/bronchial, urethral and vascular obstructions wherein the lumen of a body passageway is expanded. Thus, macrocyclic lactone II, designated as ER 803064, was prepared via a multistep synthetic sequence with included a macrolactonization reaction of III to form the desired lactone ring. The

prepared macrocycles were assayed for their effect on TNF- α and β -actin placental alkaline phosphatase transcription using human acute monocytic leukemia cells.

IT 603045-43-8P, NF 2306 603959-48-4P 603959-63-3P
603985-29-1P, NF 1535

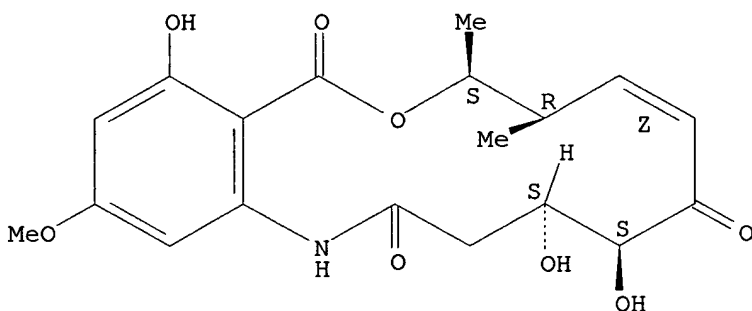
RL: COS (Cosmetic use); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of macrocyclic compds. for use in pharmaceutical and cosmetic compns. which regulate various genes involved in immune and inflammatory responses)

RN 603045-43-8 CAPLUS

CN 2H-11,1-Benzoxaazacyclotetradecine-2,6,12(1H,3H)-trione,
4,5,9,10-tetrahydro-4,5,13-trihydroxy-15-methoxy-9,10-dimethyl-,
(4S,5S,7Z,9R,10S)- (9CI) (CA INDEX NAME)

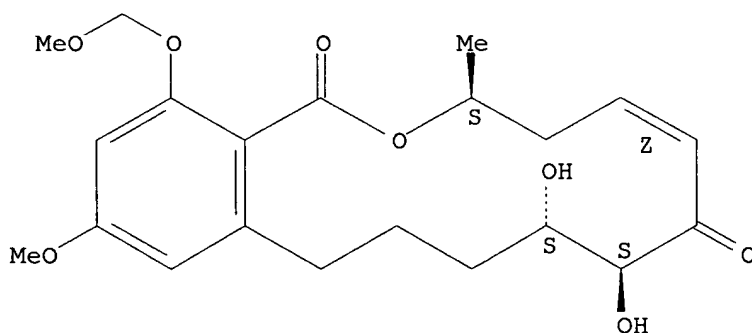
Absolute stereochemistry.
Double bond geometry as shown.



RN 603959-48-4 CAPLUS

CN 1H-2-Benzoxacyclotetradecin-1,7(8H)-dione, 3,4,9,10,11,12-hexahydro-8,9-dihydroxy-14-methoxy-16-(methoxymethoxy)-3-methyl-, (3S,5Z,8S,9S)- (9CI)
(CA INDEX NAME)

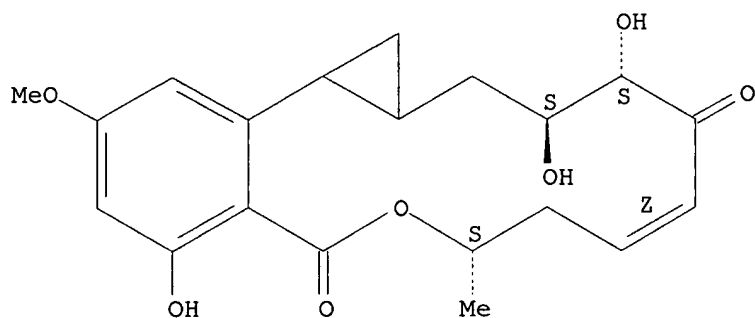
Absolute stereochemistry.
Double bond geometry as shown.



RN 603959-63-3 CAPLUS

CN Benzo[c]cycloprop[*e*]oxacyclotetradecin-5,11-dione, 7,8,12,13,14,14a,15,15a-octahydro-4,12,13-trihydroxy-2-methoxy-7-methyl-, (7S,9Z,12S,13S)- (9CI)
(CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

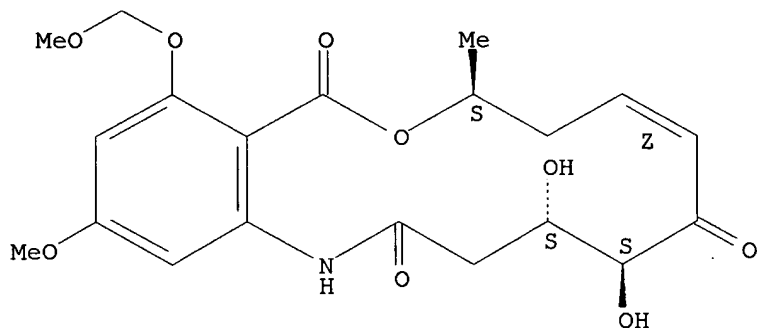


RN 603985-29-1 CAPLUS

CN 2H-11,1-Benzoxaazacyclotetradecine-2,6,12(1H,3H)-trione,
4,5,9,10-tetrahydro-4,5-dihydroxy-15-methoxy-13-(methoxymethoxy)-10-methyl-
, (4S,5S,7Z,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry as shown.



IT 603985-32-6P, NF 1537

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)

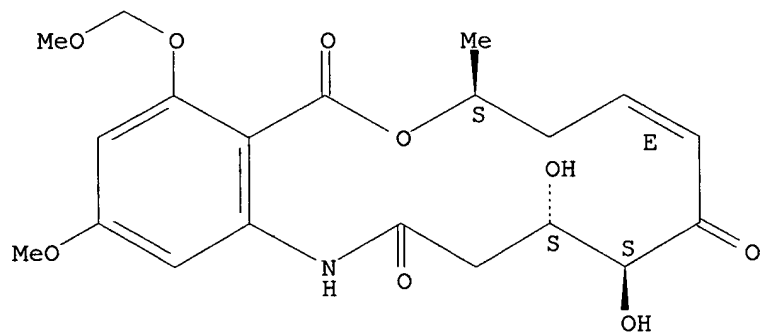
(preparation of macrocyclic compds. for use in pharmaceutical and cosmetic
compns. which regulate various genes involved in immune and
inflammatory responses)

RN 603985-32-6 CAPLUS

CN 2H-11,1-Benzoxaazacyclotetradecine-2,6,12(1H,3H)-trione,
4,5,9,10-tetrahydro-4,5-dihydroxy-15-methoxy-13-(methoxymethoxy)-10-methyl-
, (4S,5S,7E,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry as described by E or Z.



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 6 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:465995 CAPLUS

DOCUMENT NUMBER: 137:28332

TITLE: Takl inhibitors

INVENTOR(S): Tsuchiya, Masayuki; Ohtomo, Toshihiko; Ono, Koichiro; Matsumoto, Masahiko; Ito, Tatsuya

PATENT ASSIGNEE(S): Chugai Seiyaku Kabushiki Kaisha, Japan

SOURCE: PCT Int. Appl., 24 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002048135	A1	20020620	WO 2001-JP10927	20011213
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
JP 2004292315	A2	20041021	JP 2000-379995	20001214
AU 2002022627	A5	20020624	AU 2002-22627	20011213
PRIORITY APPLN. INFO.:			JP 2000-379995	A 20001214
			WO 2001-JP10927	W 20011213

AB TAK1 inhibitors or TAK1 activation inhibitors containing as the active ingredient zearalenones having hydroxyl groups at both of the 8- and 9-positions; a method of inhibiting TAK1 or a method of inhibiting the activation of TAK1 by using as the active ingredient zearalenones having hydroxyl groups at both of the 8- and 9-positions; utilization of zearalenones having hydroxyl groups at both of the 8- and 9-positions for producing TAK1 inhibitors or TAK1 activation inhibitors; and kits for inhibiting TAK1 or kits for inhibiting the activation of TAK1 containing zearalenones having hydroxyl groups at both of the 8- and 9-position and a manual.

IT 219861-66-2 437611-54-6

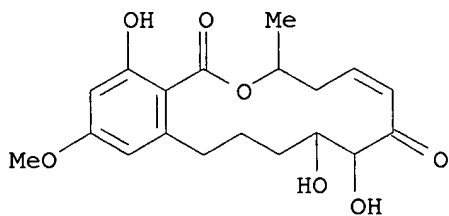
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)

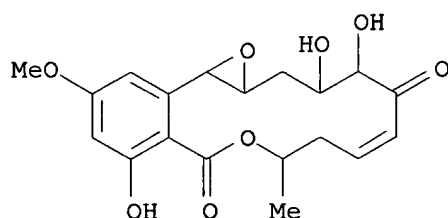
(zearalenones as Takl inhibitors for treatment of related diseases)

RN 219861-66-2 CAPLUS

CN 1H-2-Benzoxacyclotetradecin-1,7(8H)-dione, 3,4,9,10,11,12-hexahydro-8,9,16-trihydroxy-14-methoxy-3-methyl- (9CI) (CA INDEX NAME)

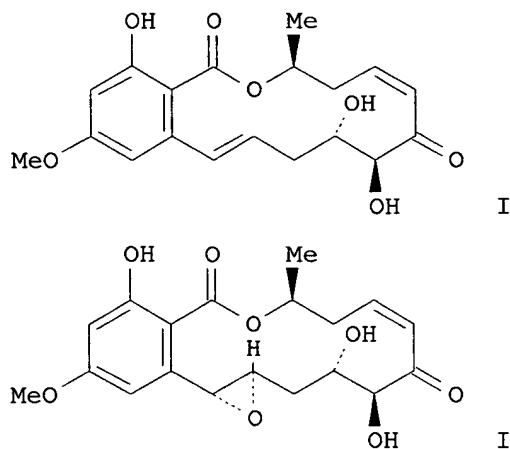


RN 437611-54-6 CAPLUS
 CN 3H-Oxireno[k][2]benzoxacyclotetradecin-5,11(2H,4H)-dione,
 1a,8,9,15b-tetrahydro-3,4,12-trihydroxy-14-methoxy-9-methyl- (9CI) (CA
 INDEX NAME)



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 7 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2002:456594 CAPLUS
 DOCUMENT NUMBER: 137:247530
 TITLE: Convergent stereospecific synthesis of LL-Z1640-2 (or
 C292), hypothemycin and related macrolides. Part 2
 AUTHOR(S): Selles, Patrice; Lett, Robert
 CORPORATE SOURCE: Unite Mixte, CNRS-AVENTIS Pharma, Romainville, 93235,
 Fr.
 SOURCE: Tetrahedron Letters (2002), 43(26), 4627-4631
 CODEN: TELEAY; ISSN: 0040-4039
 PUBLISHER: Elsevier Science Ltd.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 137:247530
 GI



AB The total syntheses of C292 (or LL-Z1640-2, I) and hypothemycin (II) have
 been achieved. The 14-membered ring formation was achieved either via an
 intramol. Suzuki coupling or much more efficiently via a Mitsunobu
 macrolactonization. Reaction conditions were found to preserve the Z
 enone present in the targets. Selective epoxidn. of C292 (I) afforded
 hypothemycin (II).

IT 76958-67-3P

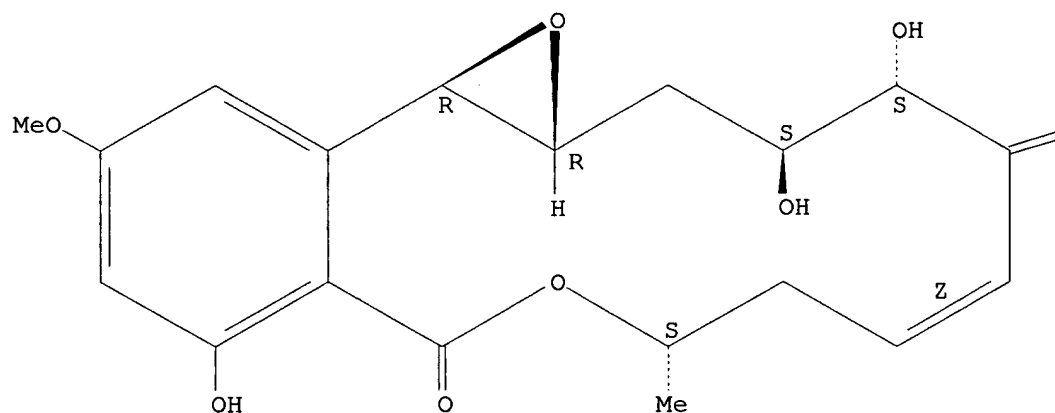
RL: SPN (Synthetic preparation); PREP (Preparation)
(convergent stereospecific synthesis of C292, hypothemycin and related
macrolides)

RN 76958-67-3 CAPLUS

CN 3H-Oxireno[k][2]benzoxacyclotetradecin-5,11(2H,4H)-dione,
1a,8,9,15b-tetrahydro-3,4,12-trihydroxy-14-methoxy-9-methyl-,
(1aR,3S,4S,6Z,9S,15bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

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REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:101776 CAPLUS

DOCUMENT NUMBER: 136:321761

TITLE: Aigialomycins A-E, new resorcylic macrolides from the
marine mangrove fungus Aigialus parvus

AUTHOR(S): Isaka, Masahiko; Suyarnsestakorn, Chotika;
Tanticharoen, Morakot; Kongsaree, Palangpon;
Thebtaranonth, Yodhathai

CORPORATE SOURCE: National Center for Genetic Engineering and
Biotechnology (BIOTEC), National Science and
Technology Development Agency (NSTDA), Bangkok, 10400,
Thailand

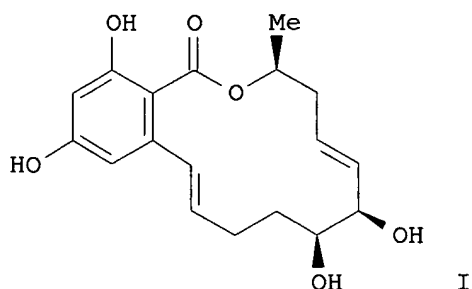
SOURCE: Journal of Organic Chemistry (2002), 67(5), 1561-1566
CODEN: JOCEAH; ISSN: 0022-3263

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



AB Aigialomycins A-E, new 14-membered resorcylic macrolides, were isolated, together with hypothemycin, from the mangrove fungus *Aigialus parvus* BCC 5311. Structures of these compds., including absolute configuration, were elucidated by spectroscopic methods, chemical conversions, and X-ray crystallog. anal. Hypothemycin and aigialomycin D (I) exhibited in vitro antimalarial activity with IC50 values of 2.2 and 6.6 $\mu\text{g/mL}$, resp., while other analogs were inactive. Cytotoxicities of these compds. were also evaluated.

IT **412328-17-7P**, Aigialomycin A

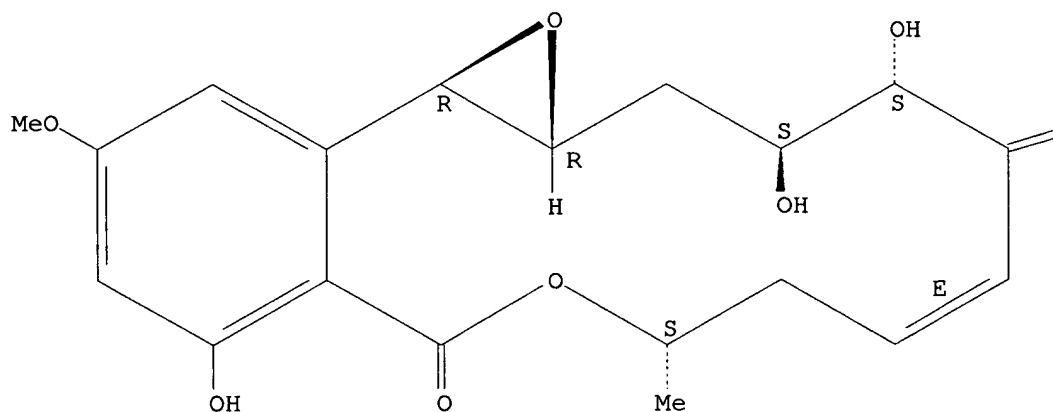
RL: BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation) (aigialomycins A-E, new resorcylic macrolides from the marine mangrove fungus *Aigialus parvus*)

RN 412328-17-7 CAPLUS

CN 3H-Oxireno[k] [2]benzoxacyclotetradecin-5,11(2H,4H)-dione, 1a,8,9,15b-tetrahydro-3,4,12-trihydroxy-14-methoxy-9-methyl-, (1aR,3S,4S,6E,9S,15bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as described by E or Z.

PAGE 1-A



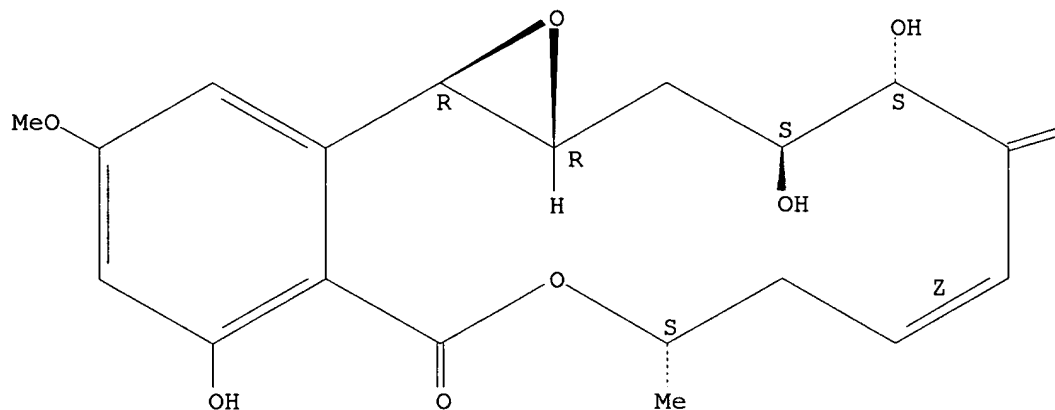
PAGE 1-B

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IT 76958-67-3, Hypothemycin
 RL: BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)
 (macrolides from the marine mangrove fungus Aigialus parvus)
 RN 76958-67-3 CAPLUS
 CN 3H-Oxireno[k][2]benzoxacyclotetradecin-5,11(2H,4H)-dione,
 1a,8,9,15b-tetrahydro-3,4,12-trihydroxy-14-methoxy-9-methyl-,
 (1aR,3S,4S,6Z,9S,15bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
 Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

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REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 9 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2001:380438 CAPLUS
 DOCUMENT NUMBER: 135:24657
 TITLE: Selective cellular targeting: multifunctional delivery vehicles
 INVENTOR(S): Glazier, Arnold
 PATENT ASSIGNEE(S): Drug Innovation & Design, Inc., USA
 SOURCE: PCT Int. Appl., 981 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001036003	A2	20010525	WO 2000-US31262	20001114
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,				

LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2391534 AA 20010525 CA 2000-2391534 20001114
AU 2001016075 A5 20010530 AU 2001-16075 20001114
EP 1255567 A1 20021113 EP 2000-978631 20001114

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

US 2003138432 A1 20030724 US 2000-738625 20001215

PRIORITY APPLN. INFO.:

US 1999-165485P P 19991115
US 2000-239478P P 20001011
US 2000-241937P P 20001020
WO 2000-US31262 W 20001114
US 2000-712465 B1 20001115

AB The present invention relates to the compns., methods, and applications of a novel approach to selective cellular targeting. The purpose of this invention is to enable the selective delivery and/or selective activation of effector mols. to target cells for diagnostic or therapeutic purposes. The present invention relates to multi-functional prodrugs or targeting vehicles wherein each functionality is capable of enhancing targeting selectivity, affinity, intracellular transport, activation or detoxification. The present invention also relates to ultralow dose, multiple target, multiple drug chemotherapy and targeted immunotherapy for cancer treatment.

IT **341552-13-4P**

RL: PNU (Preparation, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

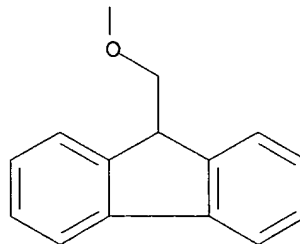
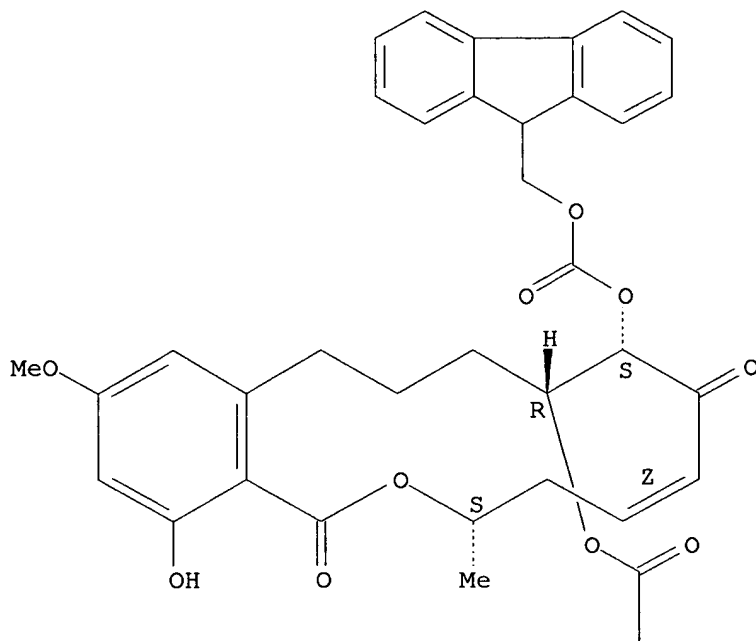
(multifunctional delivery vehicles for selective cellular targeting of drugs)

RN 341552-13-4 CAPLUS

CN Carbonic acid, (3S,5Z,8S,9R)-3,4,7,8,9,10,11,12-octahydro-16-hydroxy-14-methoxy-3-methyl-1,7-dioxo-1H-2-benzoxacyclotetradecin-8,9-diyl bis(9H-fluoren-9-ylmethyl) ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry as shown.



L3 ANSWER 10 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2000:820950 CAPLUS
 DOCUMENT NUMBER: 134:360851
 TITLE: Chemical inducers for morphological reversion of
 oncogenically transformed NIH3T3 cells
 AUTHOR(S): Sonoda, Hikaru; Omi, Kazuo
 CORPORATE SOURCE: Diagnostics Science Division, Shionogi Research
 Laboratories, Shionogi and Co., Ltd., Osaka, 553-0002,
 Japan
 SOURCE: Shionogi Kenkyusho Nenpo (2000), 50, 1-18
 CODEN: SKNEA7; ISSN: 0559-8680
 PUBLISHER: Shionogi Seiyaku K.K. Chuo Kenkyusho
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English
 AB A review with 96 refs. In the course of screening for antitumor drugs by
 using oncogene-transformed NIH3T3 cells, several compds., including
 trichostatin A, trapoxins, depudecin, oxamflatin, hypothemycin,
 geldanamycin and radicicol, have been found to cause reversion of the
 spindled morphol. of the transformed cells to the flat type. Mechanistic
 studies on these compds. have revealed that some share modes of action on

the inhibition of cellular transformation. Trichostatin A, trapoxins, depudecin and oxamflatin inhibit histone deacetylase activity. Hypothemycin, which has several structural analogs of natural origin, can inhibit MEK [not defined] family kinases. Geldanamycin and radicicol can bind to the mol. chaperone Hsp90 and accelerate the degradation of its partner proteins. This article gives an overview of the antitransformation activities of these compds. and discusses how these inhibitors of histone deacetylase, MEK family kinases and Hsp90 protein chaperone can suppress the transformation triggered by oncogenes such as v-ras and v-raf.

IT 76958-67-3, Hypothemycin

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(morphol. reversion of oncogenically transformed NIH3T3 cells by)

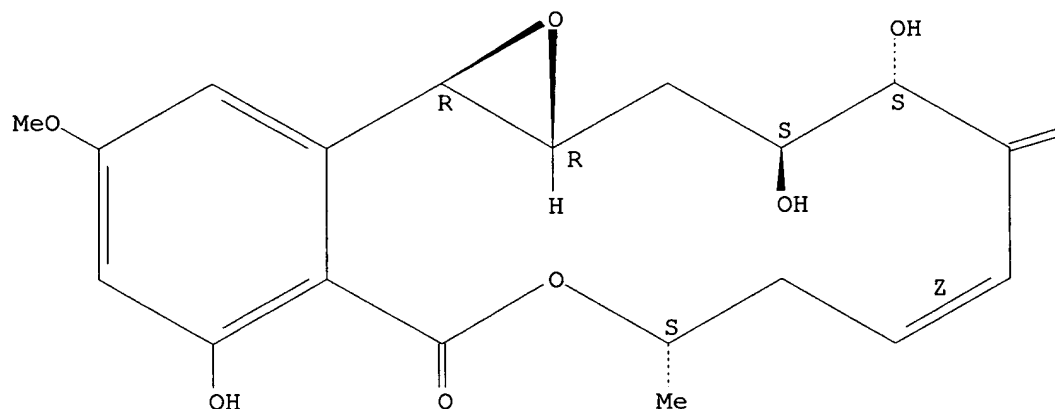
RN 76958-67-3 CAPLUS

CN 3H-Oxireno[k][2]benzoxacyclotetradecin-5,11(2H,4H)-dione,
1a,8,9,15b-tetrahydro-3,4,12-trihydroxy-14-methoxy-9-methyl-,
(1aR,3S,4S,6Z,9S,15bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

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REFERENCE COUNT: 82 THERE ARE 82 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 11 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:17527 CAPLUS

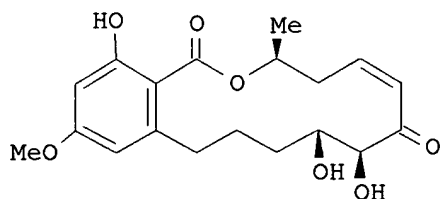
DOCUMENT NUMBER: 132:191536

TITLE: Resorcylic acid lactones: naturally occurring potent and selective inhibitors of MEK

AUTHOR(S): Zhao, Annie; Lee, Seok H.; Mojena, Marina; Jenkins, Rosalind G.; Patrick, Denis R.; Huber, Hans E.; Goetz, Michael A.; Hensens, Otto D.; Zink, Deborah L.; Vilella, Dolores; Dombrowski, Anne W.; Lingham, Russell B.; Huang, Leeyuan

CORPORATE SOURCE: Merck Research Laboratories, Rahway, NJ, 07065, USA

SOURCE: Journal of Antibiotics (1999), 52(12), 1086-1094
 CODEN: JANTAJ; ISSN: 0021-8820
 PUBLISHER: Japan Antibiotics Research Association
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 GI



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AB A resorcylic acid lactone, L-783,277 (I), isolated from a *Phoma* sp. (ATCC 74403) which came from the fruitbody of *Helvella acetabulum*, is a potent and specific inhibitor of MEK (Map kinase kinase). L-783,277 inhibits MEK with an IC₅₀ value of 4 nM. It weakly inhibits Lck and is inactive against Raf, PKA and PKC. L-783,277 is an irreversible inhibitor of MEK and is competitive with respect to ATP. L-783,290, the trans-isomer of L-783,277, was isolated from the same culture and evaluated together with several semi-synthetic resorcylic acid lactone analogs. A preliminary structure-activity relationship is presented. Several independent cell-based assays have been carried out to study the biol. activities of these resorcylic acid lactone compds. and a brief result summary from these studies is presented.

IT 219917-92-7P, L 783277

RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); RCT (Reactant); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); RACT (Reactant or reagent)
 (isolation, structure and bioactivity of L-783,277, a resorcylic acid lactone isolated from a *Phoma* sp.)

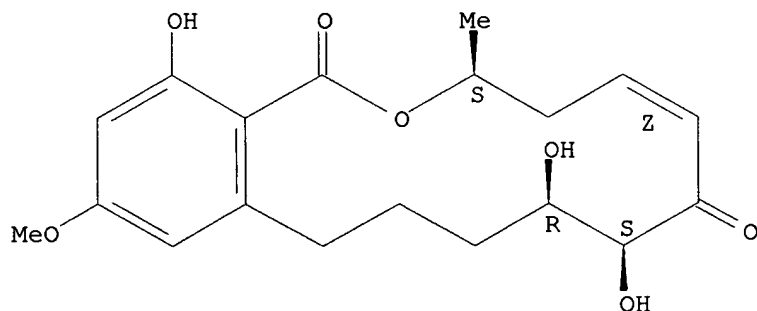
RN 219917-92-7 CAPLUS

CN 1H-2-Benzoxacyclotetradecin-1,7(8H)-dione, 3,4,9,10,11,12-hexahydro-8,9,16-trihydroxy-14-methoxy-3-methyl-, (3R,5Z,8R,9S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

Double bond geometry as shown.

Currently available stereo shown.



IT 219917-93-8P, L 783290

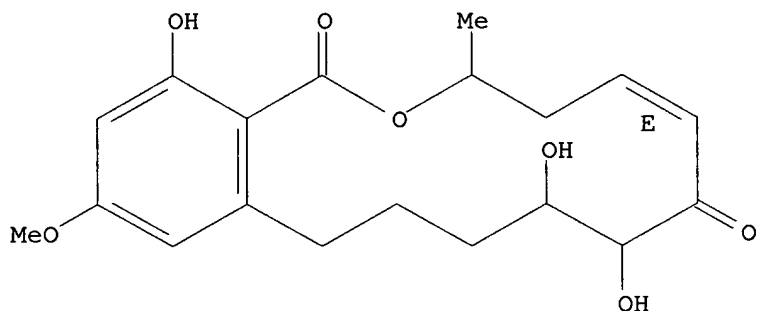
RL: BAC (Biological activity or effector, except adverse); BOC (Biological

occurrence); BSU (Biological study, unclassified); PUR (Purification or recovery); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation) (isolation, structure and bioactivity of L-783,277, a resorcylic acid lactone isolated from a Phoma sp.)

RN 219917-93-8 CAPLUS

CN 1H-2-Benzoxacyclotetradecin-1,7(8H)-dione, 3,4,9,10,11,12-hexahydro-8,9,16-trihydroxy-14-methoxy-3-methyl-, (5E)- (9CI) (CA INDEX NAME)

Double bond geometry as described by E or Z.
Currently available stereo shown.



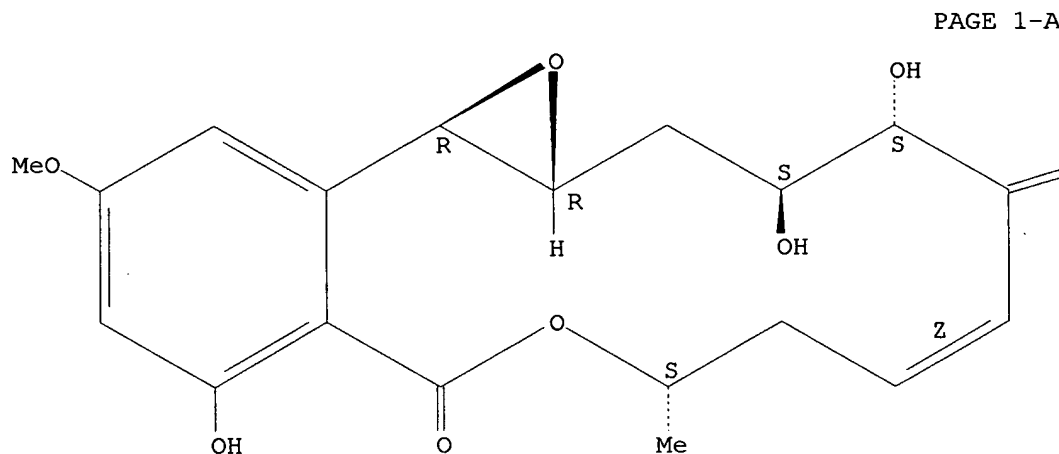
IT 76958-67-3, Hypothemycin

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study) (isolation, structure and bioactivity of L-783,277, a resorcylic acid lactone isolated from a Phoma sp.)

RN 76958-67-3 CAPLUS

CN 3H-Oxireno[k][2]benzoxacyclotetradecin-5,11(2H,4H)-dione, 1a,8,9,15b-tetrahydro-3,4,12-trihydroxy-14-methoxy-9-methyl-, (1aR,3S,4S,6Z,9S,15bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



PAGE 1-A

PAGE 1-B

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REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 12 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:17526 CAPLUS

DOCUMENT NUMBER: 132:179619

TITLE: Production of a family of kinase-inhibiting lactones from fungal fermentations

AUTHOR(S): Dombrowski, Anne; Jenkins, Rosalind; Raghoobar, Susan; Bills, Gerald; Polishook, Jon; Pelaez, Fernando; Burgess, Bruce; Zhao, Annie; Huang, Leeyuan; Zhang, Yan; Goetz, Michael

CORPORATE SOURCE: Merck Research Laboratories, Rahway, NJ, 07065, USA

SOURCE: Journal of Antibiotics (1999), 52(12), 1077-1088

CODEN: JANTAJ; ISSN: 0021-8820

PUBLISHER: Japan Antibiotics Research Association

DOCUMENT TYPE: Journal

LANGUAGE: English

AB During the course of screening for natural products from fungi, exts. of several cultures were found to make a family of related resorcylic acid lactone compds., which are potent inhibitors of MEK kinase. Comparative and empirical studies of fermentation conditions improved the titers of the compds. of interest. Striking changes in the ratios and amts. of the major and minor compds. in some cases were achieved by manipulations of media composition

IT 219917-93-8P

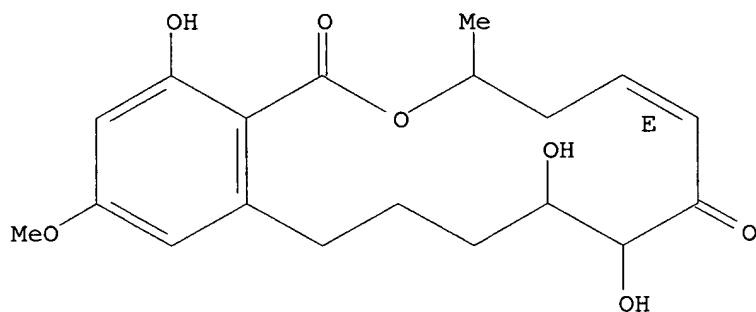
RL: BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)

(L 783290; production of a family of kinase-inhibiting lactones from fungal fermns.)

RN 219917-93-8 CAPLUS

CN 1H-2-Benzoxacyclotetradecin-1,7(8H)-dione, 3,4,9,10,11,12-hexahydro-8,9,16-trihydroxy-14-methoxy-3-methyl-, (5E)- (9CI) (CA INDEX NAME)

Double bond geometry as described by E or Z.
Currently available stereo shown.



IT 219917-92-7P, L 783277

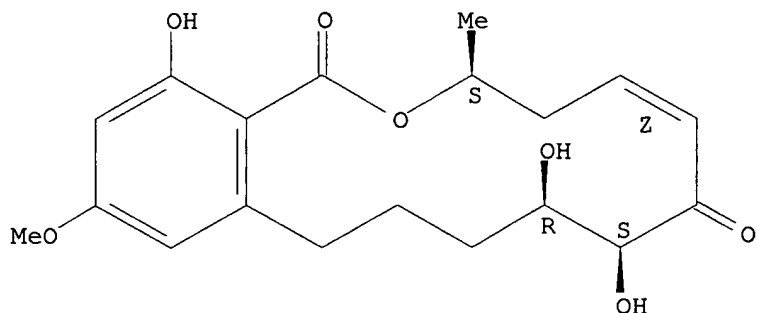
RL: BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)

(production of a family of kinase-inhibiting lactones from fungal fermns.)

RN 219917-92-7 CAPLUS

CN 1H-2-Benzoxacyclotetradecin-1,7(8H)-dione, 3,4,9,10,11,12-hexahydro-8,9,16-trihydroxy-14-methoxy-3-methyl-, (3R,5Z,8R,9S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry as shown.
Currently available stereo shown.



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 13 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:812900 CAPLUS

DOCUMENT NUMBER: 132:117243

TITLE: Antitumor efficacy of hypothemycin, A new ras-signaling inhibitor

AUTHOR(S): Tanaka, Hidekazu; Nishida, Kazuyo; Sugita, Kenji; Yoshioka, Takayuki

CORPORATE SOURCE: Shionogi Research Laboratories, Shionogi and Co., Ltd., Osaka, 553-0002, Japan

SOURCE: Japanese Journal of Cancer Research (1999), 90(10), 1139-1145

CODEN: JJCREP; ISSN: 0910-5050

PUBLISHER: Japanese Cancer Association

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We have devised a new drug screening assay to discover anti-cancer drugs which inhibit Ras-mediated cellular signals, by utilizing a Ras-responsive element (RRE)-driven reporter gene system. We found that hypothemycin, an anti-bacterial, reduces RRE-dependent transcription. Treatment of tumor cells with hypothemycin resulted in reduced expression of Ras-inducible genes, including MMP (matrix metalloproteinase)-1, MMP-9, transforming growth factor- β (TGF- β), and vascular endothelial growth factor (VEGF), but not that of the constitutively expressed gene, MMP-2. The results of zymog. demonstrated that hypothemycin reduced the production of MMP-9 and MMP-3, another Ras-inducible MMP, in the culture medium. Hypothemycin selectively inhibits anchorage-independent growth of Ras-transformed cells in comparison with anchorage-dependent growth. These findings suggest that hypothemycin inhibits Ras-mediated cellular signaling. Daily treatment of tumor-bearing mice with hypothemycin resulted in significant inhibition of tumor growth. Since MMP-1, MMP-3 and MMP-9 play important roles in tumor invasion and TGF- β and VEGF are involved in tumor angiogenesis, hypothemycin is considered to be an example of a new class of antitumor drugs, whose antitumor efficacy can be at least partly attributed to inhibition of Ras-inducible genes.

IT 76958-67-3, Hypothemycin

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

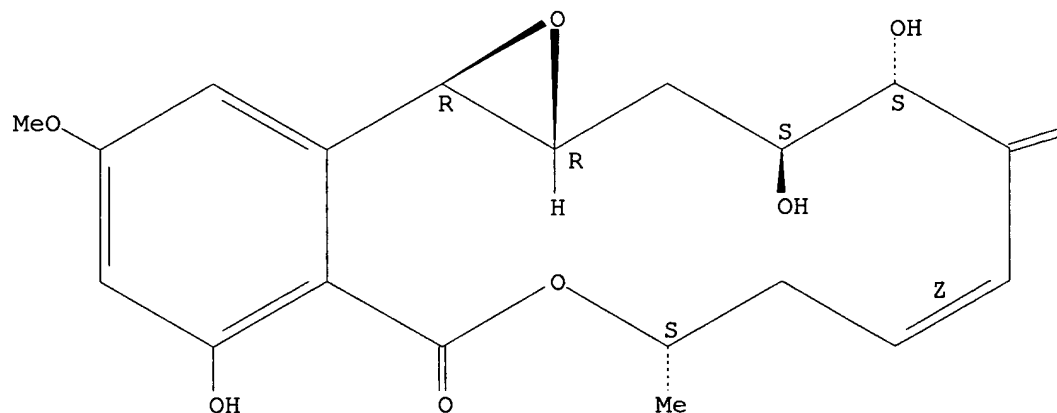
(antitumor efficacy of hypothemycin, a new ras-signaling inhibitor)

RN 76958-67-3 CAPLUS

CN 3H-Oxireno[k][2]benzoxacyclotetradecin-5,11(2H,4H)-dione, 1a,8,9,15b-tetrahydro-3,4,12-trihydroxy-14-methoxy-9-methyl-, (1aR,3S,4S,6Z,9S,15bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

Double bond geometry as shown.



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REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 14 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:806935 CAPLUS

DOCUMENT NUMBER: 132:132003

TITLE: Hypothemycin inhibits the proliferative response and modulates the production of cytokines during T cell activation

AUTHOR(S): Camacho, R.; Staruch, M. J.; DaSilva, C.; Koprak, S.; Sewell, T.; Salituro, G.; Dumont, F. J.

CORPORATE SOURCE: Rm. 80W107, Department of Immunology and Rheumatology, Merck Research Laboratories, Rahway, NJ, USA

SOURCE: Immunopharmacology (1999), 44(3), 255-265

CODEN: IMMUDP; ISSN: 0162-3109

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

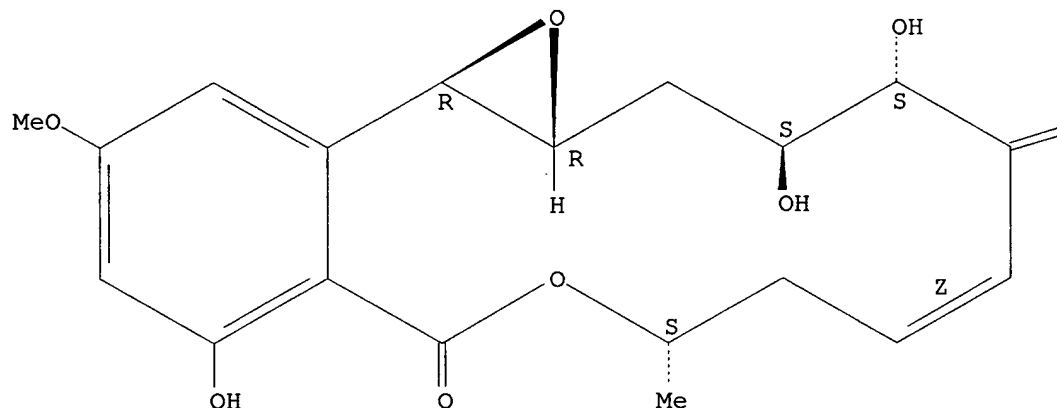
LANGUAGE: English

AB Hypothemycin, a resorcylic acid lactone antibiotic, was identified as active in a screen for inhibitors of T cell activation. It was found to inhibit the proliferation of mouse and human T cells stimulated with anti-CD3 mAb+PMA and of human PBMC stimulated with anti-CD3 mAb alone. This inhibition was partially reversed by exogenous IL-2 indicating that it is not due to non-specific toxicity. Hypothemycin potently suppressed the production of IL-2 (IC50: 9 nM) but affected IL-2-induced proliferation to a lesser extent (IC50: 194 nM). Hypothemycin also inhibited IL-6, IL-10, IFN- γ and TNF- α production. By contrast, it markedly enhanced the production of IL-4, IL-5 and IL-13. These effects were seen both at the mRNA and protein secretion levels. Anal. of the effect of hypothemycin on CD69 induction suggested that it disrupts calcineurin-independent rather than calcineurin-dependent signaling. Furthermore, hypothemycin was able to inhibit the phosphorylation of ERK1/2 induced by PMA treatment of T cells. Therefore, hypothemycin represents an inhibitor of T cell activation with a novel mode of action and unique modulatory activity on cytokine production

IT 76958-67-3, Hypothemycin
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
 (hypothemycin inhibition of proliferative response and modulation of cytokine production during T cell activation)
 RN 76958-67-3 CAPLUS
 CN 3H-Oxireno[k][2]benzoxacyclotetradecin-5,11(2H,4H)-dione,
 1a,8,9,15b-tetrahydro-3,4,12-trihydroxy-14-methoxy-9-methyl-,
 (1aR,3S,4S,6Z,9S,15bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
 Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

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REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 15 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 1999:428696 CAPLUS
 DOCUMENT NUMBER: 131:193819
 TITLE: Suppression of oncogenic transformation by hypothemycin associated with accelerated cyclin D1 degradation through ubiquitin-proteasome pathway
 AUTHOR(S): Sonoda, Hikaru; Omi, Kazuo; Hojo, Kanji; Nishida, Kazuyo; Omura, Satoshi; Sugita, Kenji
 CORPORATE SOURCE: Shionogi Research Laboratories, Shionogi & Co., Ltd., Osaka, 553-0002, Japan
 SOURCE: Life Sciences (1999), 65(4), 381-394
 CODEN: LIFSAK; ISSN: 0024-3205
 PUBLISHER: Elsevier Science Inc.
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Hypothemycin was originally isolated as an antifungal metabolite of *Hypomyces trichothecoides*. Here we report that treatment on v-K-ras-transformed NIH3T3 cells (DT cells) with hypothemycin caused drastic decrease in amount of cyclin D1 protein with concomitant

prolongation of G1 phase in their cell cycle. Anal. using hypothemycin-resistant mutant of *Schizosaccharomyces pombe* (*S. pombe*) was carried out to show that *S. pombe* rhp6+ (homolog of *Saccharomyces cerevisiae* RAD6) and mammalian ubiquitin-conjugating enzyme 2 (ubc2) are the targets of hypothemycin or its downstream mols. in ubiquitin-conjugation process. Furthermore, in the presence of lactacystin, a specific inhibitor for proteasome, hypothemycin greatly enhanced the accumulation of multi-ubiquitinated form of cyclin D1 in DT cells. Therefore, it is indicated that hypothemycin facilitates ubiquitinating process of cyclin D1. In terms of malignant phenotype, hypothemycin inhibited anchorage-independent growth and reverted the morphol. of DT cells. On the contrary, their morphol. still remained transformed in the addnl. presence of lactacystin. Our results suggest that cyclin D1 is a key mol. working downstream in ras-signaling and that the transformation can be inhibited by the compound which can activate ubiquitin-proteasome pathway including degradation of cyclin D1.

IT 76958-67-3, Hypothemycin

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(suppression of oncogenic transformation by hypothemycin associated with accelerated cyclin D1 degradation through ubiquitin-proteasome pathway)

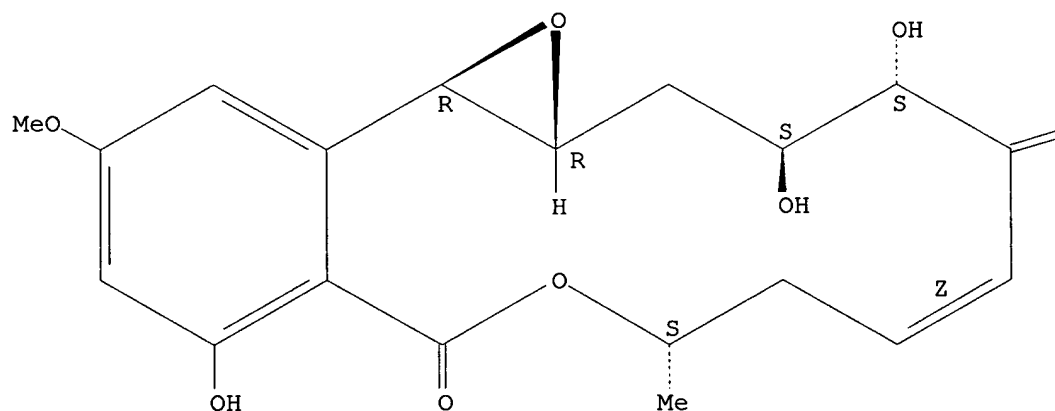
RN 76958-67-3 CAPLUS

CN 3H-Oxireno[k][2]benzoxacyclotetradecin-5,11(2H,4H)-dione, 1a,8,9,15b-tetrahydro-3,4,12-trihydroxy-14-methoxy-9-methyl-, (1aR,3S,4S,6Z,9S,15bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

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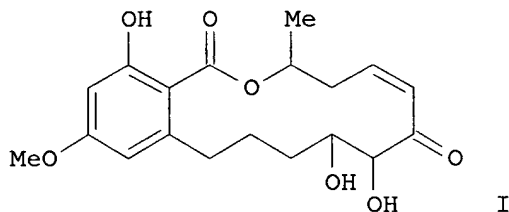
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 16 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:59266 CAPLUS

DOCUMENT NUMBER: 130:119613
 TITLE: MAPK/Erk kinase (MEK)-inhibiting lactones, production thereof from Phoma, and therapeutic use
 INVENTOR(S): Bills, Gerald F.; Diez, Maria Teresa; Dombrowski, Anne W.; Falconi, Nicole D.; Goetz, Michael A.; Heimbrook, David C.; Hensens, Otto D.; Huang, Leeyuan; Huber, Hans E.; Jenkins, Rosalind G.; Kendall, Richard L.; Lee, Seok H.; Mojena, Marina; Oliff, Allen I.; Patrick, Denis R.; Pelaez, Fernando; Thomas, Kenneth A., Jr.; Vilella, Dolores; Zhao, Annie Z.; Zink, Deborah L.
 PATENT ASSIGNEE(S): Merck and Co., Inc., USA
 SOURCE: Brit. UK Pat. Appl., 30 pp.
 CODEN: BAXXDU
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 2323845	A1	19981007	GB 1998-6929	19980331
PRIORITY APPLN. INFO.:			US 1997-42875P	P 19970331
			GB 1997-9292	A 19970507

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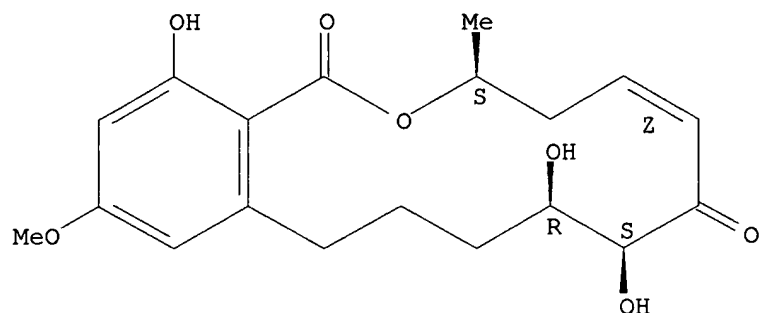
AB Compds. I are disclosed. I can be used for treating cancer and ocular disease, e.g. diabetic retinopathy, or other diseases where neoangiogenesis is implicated. Also disclosed is a culture of Phoma sp. which produces I, as well as a process for production of I.

IT **219917-92-7P 219917-93-8P**
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (MEK-inhibiting lactones, production from Phoma, and therapeutic use)

RN 219917-92-7 CAPLUS

CN 1H-2-Benzoxacyclotetradecin-1,7(8H)-dione, 3,4,9,10,11,12-hexahydro-8,9,16-trihydroxy-14-methoxy-3-methyl-, (3R,5Z,8R,9S)-rel- (9CI) (CA INDEX NAME)

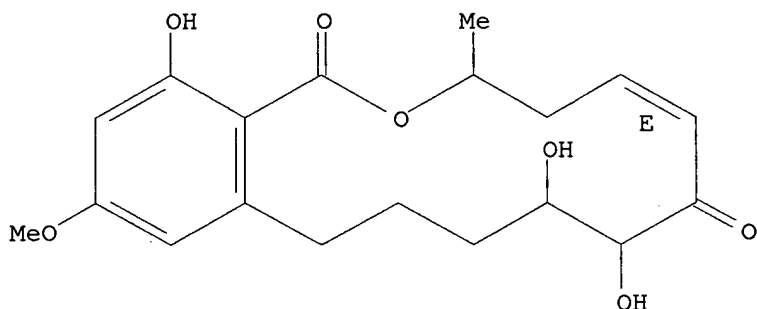
Relative stereochemistry.
 Double bond geometry as shown.
 Currently available stereo shown.



RN 219917-93-8 CAPLUS

CN 1H-2-Benzoxacyclotetradecin-1,7(8H)-dione, 3,4,9,10,11,12-hexahydro-8,9,16-trihydroxy-14-methoxy-3-methyl-, (5E)- (9CI) (CA INDEX NAME)

Double bond geometry as described by E or Z.
Currently available stereo shown.



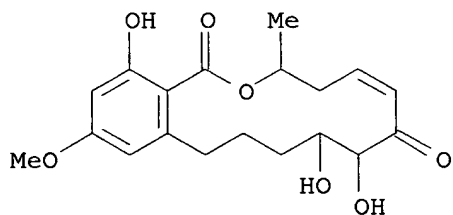
IT **219861-66-2**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(MEK-inhibiting lactones, production from Phoma, and therapeutic use)

RN 219861-66-2 CAPLUS

CN 1H-2-Benzoxacyclotetradecin-1,7(8H)-dione, 3,4,9,10,11,12-hexahydro-8,9,16-trihydroxy-14-methoxy-3-methyl- (9CI) (CA INDEX NAME)



L3 ANSWER 17 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1993:495188 CAPLUS

DOCUMENT NUMBER: 119:95188

TITLE: Revised structure and stereochemistry of hypothemycin
AUTHOR(S): Agatsuma, Tsutomu; Takahashi, Akira; Kabuto, Chizuko; Nozoe, Shigeo

CORPORATE SOURCE: Fac. Pharm. Sci., Tohoku Univ., Sendai, 980, Japan

SOURCE: Chemical & Pharmaceutical Bulletin (1993), 41(2),

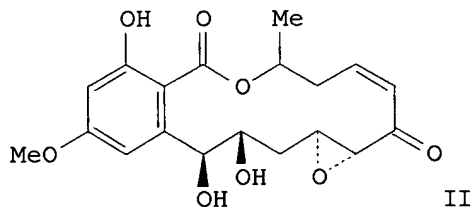
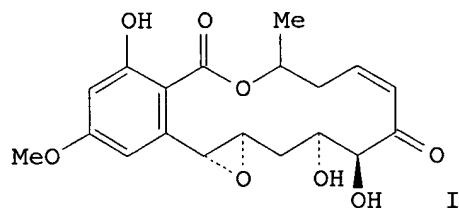
DOCUMENT TYPE:

Journal

LANGUAGE:

English

GI



AB A cytotoxic 14-membered resorcylic macrolide, isolated from *Coriolus versicolor* (L.: FR.) QUEL., was found to be identical with hypothemycin, previously isolated from *Hypomyces trichothecoides*. Based on NMR and x-ray crystal data the structure of hypothemycin has been elucidated to be I rather than the originally proposed II.

IT **76958-67-3**

RL: RCT (Reactant); RACT (Reactant or reagent)
(crystal structure, mol. structure, and absolute configuration of)

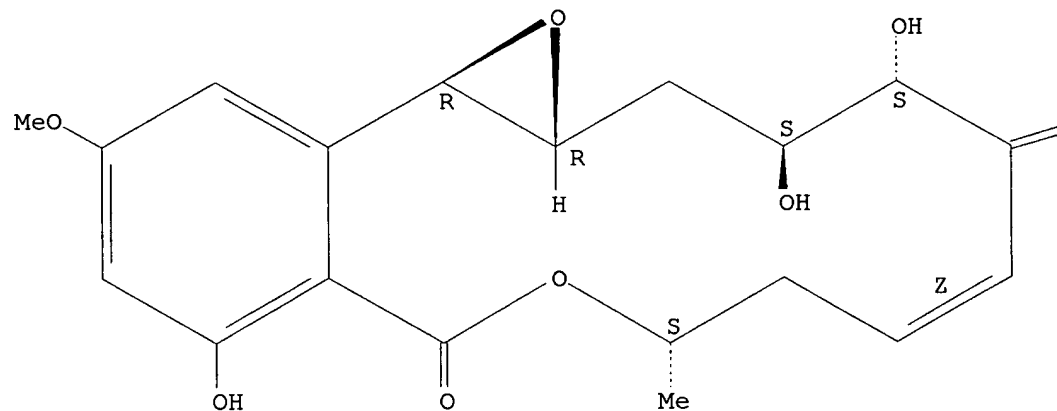
RN 76958-67-3 CAPLUS

CN 3H-Oxireno[k][2]benzoxacyclotetradecin-5,11(2H,4H)-dione,
1a,8,9,15b-tetrahydro-3,4,12-trihydroxy-14-methoxy-9-methyl-,
(1aR,3S,4S,6Z,9S,15bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

Double bond geometry as shown.

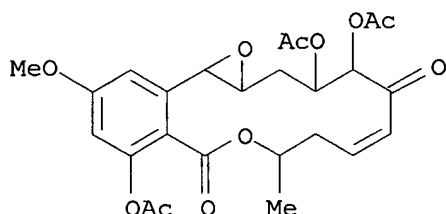
PAGE 1-A



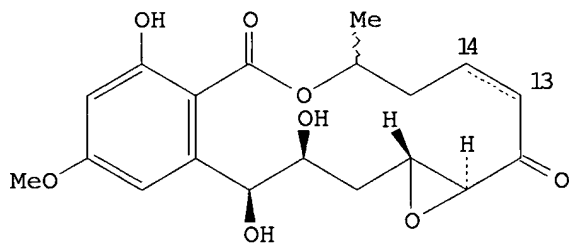
PAGE 1-B

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IT **149270-54-2P**, Hypothemycin triacetate
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (preparation of)
 RN 149270-54-2 CAPLUS
 CN 3H-Oxireno[k][2]benzoxacyclotetradecin-5,11(2H,4H)-dione,
 3,4,12-tris(acetyloxy)-1a,8,9,15b-tetrahydro-14-methoxy-9-methyl-,
 [1aR-(1aR*,3S*,4S*,6Z,9S*,15bR*)]- (9CI) (CA INDEX NAME)



L3 ANSWER 18 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 1982:31271 CAPLUS
 DOCUMENT NUMBER: 96:31271
 TITLE: Metabolites of pyrenomycetes. XIV. Structure and
 partial stereochemistry of the antibiotic macrolides
 hypothemycin and dihydrohypothemycin
 AUTHOR(S): Nair, M. S. R.; Carey, S. T.; James, J. C.
 CORPORATE SOURCE: Osborn Lab. Mar. Sci., New York Aquarium, Brooklyn,
 NY, 11224, USA
 SOURCE: Tetrahedron (1981), 37(14), 2445-9
 CODEN: TETRAB; ISSN: 0040-4020
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 GI



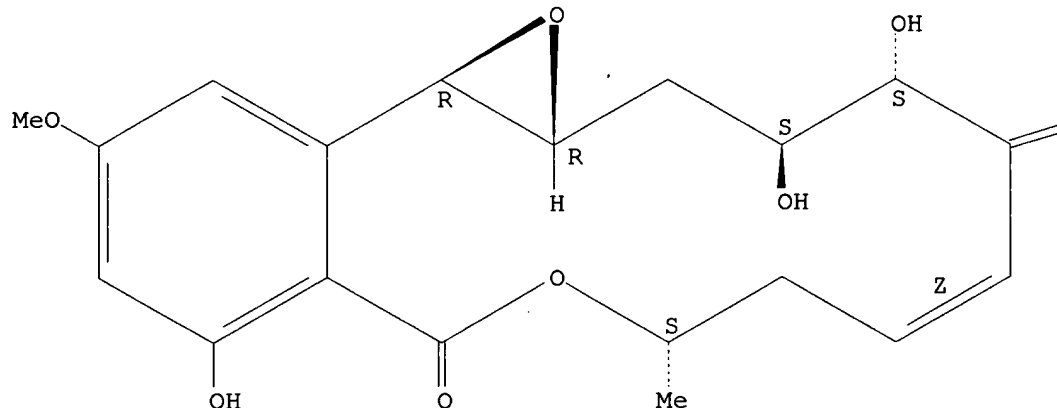
I, 13,14-unsatd.
 II, 13,14-satd.

AB The structures of hypothemycin (I) and dihydrohypothemycin (II), which
 were isolated from the fungus *Hypomyces trichothecoides*, were determined by
 spectral anal. and chemical degradation. The configurations of the macrolides
 were determined by NMR anal., particularly of the 2-dimensional J 1H spectra.
 I and II were active against *Tetrahymena furgasoni*, *Ustilago maydis*, and
Botrytis allii.

IT **76958-67-3**
 RL: BIOL (Biological study)
 (from *Hypomyces trichothecoides*, structure and configuration of)
 RN 76958-67-3 CAPLUS
 CN 3H-Oxireno[k][2]benzoxacyclotetradecin-5,11(2H,4H)-dione,
 1a,8,9,15b-tetrahydro-3,4,12-trihydroxy-14-methoxy-9-methyl-,
 (1aR,3S,4S,6Z,9S,15bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

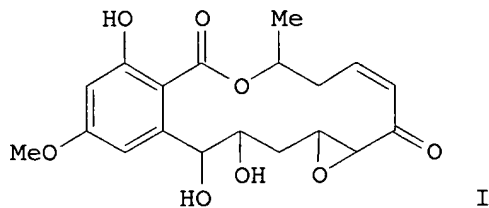
PAGE 1-A



PAGE 1-B

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L3 ANSWER 19 OF 19 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1981:117417 CAPLUS
DOCUMENT NUMBER: 94:117417
TITLE: Metabolites of pyrenomycetes. XIII. Structure of
(+)-hypothemycin, an antibiotic macrolide from
Hypomyces trichothecoides
AUTHOR(S): Nair, M. S. R.; Carey, Susan T.
CORPORATE SOURCE: New York Bot. Garden, Bronx, NY, 10458, USA
SOURCE: Tetrahedron Letters (1980), 21(21), 2011-12
CODEN: TELEAY; ISSN: 0040-4039
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



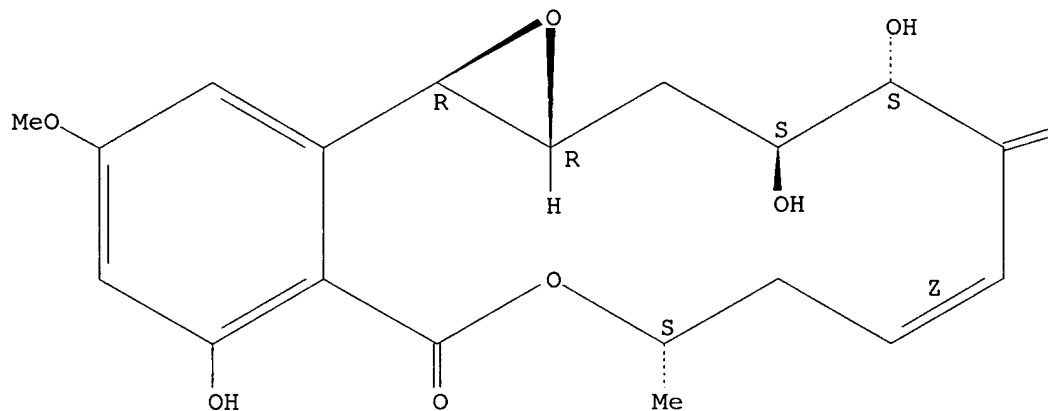
AB On chemical evidence and spectroscopic data, the structure I was assigned to
(+)-hypothemycin, a macrolide antibiotic metabolite from H.
trichothecoides, which was active against Tetrahymena furgasoni (LD50 1
ppm), and to a lesser extent against Ustilago maydis.

IT 76958-67-3
RL: BIOL (Biological study)

(from *Hypomyces tricothecoides*, structure of)
 RN 76958-67-3 CAPLUS
 CN 3H-Oxireno[k][2]benzoxacyclotetradecin-5,11(2H,4H)-dione,
 1a,8,9,15b-tetrahydro-3,4,12-trihydroxy-14-methoxy-9-methyl-,
 (1aR,3S,4S,6Z,9S,15bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
 Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

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